PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference P37825WO	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/GB2004/004336	International filing date *(day/month/year)* 13.10.2004	Priority date *(day/month/year)* 14.10.2003
International Patent Classification (IPC) or both national classification and IPC C07D209/30, A61K31/404, A61P43/00, C07D403/12, C07D401/12, C07D417/12		
Applicant OXAGEN LIMITED		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 4 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 7 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
09.05.2005	29.07.2005
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized Officer Diederen, J Telephone No. +31 70 340-1097

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB2004/004336

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-37 as originally filed

Claims, Numbers

1-30 received on 09.05.2005 with letter of 09.05.2005

Drawings, Figures

1 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

☐ the description, pages:

☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-30
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-30
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-30
	No:	Claims	

2. Citations and explanations

   see separate sheet

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following document:

D3: WO 03/066047 A (ASTRAZENECA AB) 14 August 2003 (2003-08-14)

1. Amendments (Article 34(2)(b) PCT)

The amendments filed with your letter dated 09.05.2005 are allowable with respect to Article 34(2)(b) PCT

2. Novelty and Inventive Step (Article 33(2) and 33(3) PCT

The present application fulfills the requirements of Article 33(2) and 33(3) PCT with respect to novelty and inventive step.

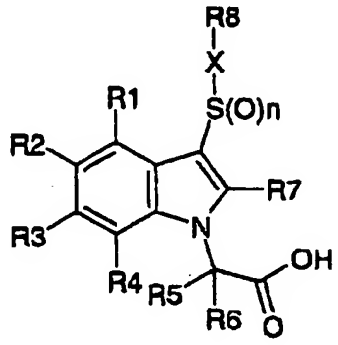
Document D3 is regarded as the closest prior art. The document discloses compounds of formula I which are used to treat diseases mediated by PGD2 (modulators of CRTh2 receptor activity). The difference of the compounds of D3 and the present application is that the compounds of D3 are substituted with a carboxymethylene group on the 3S-position of the indole, whereas the compounds of the present application bear a S(O)nR8 group and the compounds of D3 bear a 1,3-benzothiazole group at the 1-position of the indole ring where the compounds of the present application have a C(R5R6)COOH group.

The problem to be solved by the applicant was to provide alternative compounds with CRTh2 antagonist activity. A skilled person would not, starting from D3 come to the solution of the present application as he would have to change two substituents.

It is therefore considered that the subject-matter of claims 1-30 is novel and inventive over the prior art with respect to Article 33(2) and 33(3) PCT.

CLAIMS

1. A compound of general formula (I)



I

wherein

R^1, R^2, R^3 and R^4 are independently hydrogen, halo, C_1-C_6 alkyl, -O(C_1-C_6 alkyl), $-CON(R^9)_2$, $-SOR^9$, $-SO_2R^9$, $-SO_2N(R^9)_2$, $-N(R^9)_2$, $-NR^9COR^9$, $-CO_2R^9$, $-COR^9$, $-SR^9$, -OH, $-NO_2$ or -CN;

each R^9 is independently hydrogen or C_1-C_6 alkyl;

R^5 and R^6 are each independently hydrogen, or C_1-C_6 alkyl or together with the carbon atom to which they are attached form a C_3-C_7 cycloalkyl group;

R^7 is hydrogen or C_1-C_6 alkyl

n is 1 or 2;

X is a bond or, when n is 2, X may also be a NR^9 group;

wherein R^9 is as defined above;

when X is a bond R^8 is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, biphenyl or a 9-14 membered bicyclic or tricyclic heteroaryl group;

when X is a NR^9 group R^8 may additionally be phenyl, naphthyl or a 5-7 membered heteroaromatic ring; and

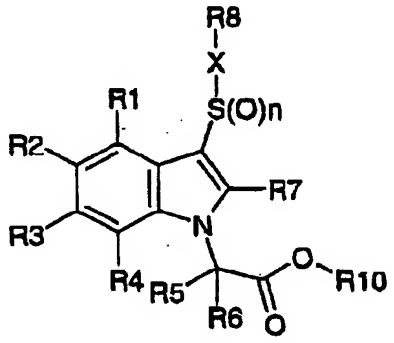
the R^8 group is optionally substituted with one or more substituents selected from halo, C_1-C_6 alkyl, -O(C_1-C_6)alkyl, aryl, -O-aryl, heteroaryl, -O-heteroaryl, $-CON(R^9)_2$, $-SOR^9$, $-SO_2R^9$, $SO_2N(R^9)_2$, $-N(R^9)_2$, $-NR^9COR^9$, $-CO_2R^9$, $-COR^9$, $-SR^9$,

-OH, -NO_2 or -CN;

wherein R^9 is as defined above;

or a pharmaceutically acceptable salt, hydrate, solvate, complex or prodrug thereof.

2. A compound of general formula (II):



II

~~wherein R^1, R^2, R^3, R^4, R^5, R^6, n, X, R^7 and R^8 are as defined for general formula (I);~~

R^{10} is C_1-C_6 alkyl, aryl, $(CH_2)_mOC(=O)C_1$-C_6alkyl, $(CH_2)_mN(R^{11})_2$, $CH((CH_2)_mO(C=O)R^{12})_2$;

m is 1 or 2;

R^{11} is hydrogen or methyl;

R^{12} is C_1-C_{18} alkyl.

3. A compound as claimed in claim 1 or claim 2 wherein, independently or in any combination:

R^1 is halo or hydrogen;

R^2 is halo or hydrogen;

R^3 is halo or hydrogen;

R^4 is halo or hydrogen.

4. A compound as claimed in any one of claims 1 to 3 wherein R^1, R^3 and R^4 are hydrogen and R^2 is halo.

5. A compound as claimed in claim 4 wherein R^2 is fluoro.

6. A compound as claimed in any one of claims 1 to 5 wherein R^5 and R^6 are each independently hydrogen or C_1-C_4 alkyl.

7. A compound as claimed in claim 6 wherein at least one of R^5 and R^6 are hydrogen.

8. A compound as claimed in claim 7 wherein both R^5 and R^6 are hydrogen.

9. A compound as claimed in any one of claims 1 to 8 wherein R^7 is H or C_1-C_6 alkyl.

10. A compound as claimed in claim 9 wherein R^7 is methyl.

11. A compound as claimed in any one of claims 1 to 10 wherein n is 2.

12. A compound as claimed in any one of claims 1 to 11 wherein X is a bond and R^8 is C_1-C_6 alkyl, biphenyl or a bicyclic heteroaryl group, any of which may be substituted with halogen, phenyl, $-CO_2R^9$ $CON(R^9)_2$ or $-SO_2R^9$, where R^9 is as defined above.

13. A compound as claimed in claim 12 wherein R^8 is C_1-C_4 alkyl, biphenyl, a bicyclic heteroaryl group or a 5-7 membered heterocyclic ring, any of which may be substituted with phenyl, $-CO_2R^9$ $CON(R^9)_2$ or $-SO_2R^9$, where R^9 is H or C_1-C_4 alkyl.

14. A compound as claimed in any one of claims 1 to 11 wherein X is NR^9, R^9 is H or methyl and R^8 is:

phenyl optionally substituted with one or more halo, C_1-C_6 alkyl or $-O(C_1$-C_6 alkyl) groups;

C_1-C_6 alkyl, optionally substituted with aryl; or
heteroaryl.

15. A compound as claimed in claim 14, wherein R^8 is phenyl, benzyl or pyridyl, any of which may optionally be substituted with one or more halo, methyl or methoxy groups.

16. [3-(Butane-1-sulfonyl)-5-fluoro-2-methyl-indol-1-yl]-acetic acid
3-(Biphenyl-4-sulfonyl)-5-fluoro-2-methyl-indol-1-yl]-acetic acid
(3-Carboxymethanesulfonyl-5-fluoro-2-methyl-indol-1-yl)-acetic acid
(3-Carbamoylmethanesulfonyl-5-fluoro-2-methyl-indol-1-yl)-acetic acid
[5-Fluoro-3-(2-methanesulfonyl-ethanesulfonyl)-2-methyl-indol-1-yl]-acetic acid
[3-(Benzothiazole-2-sulfonyl)-5-fluoro-2-methyl-indol-1-yl]-acetic acid
[3-(Benzothiazole-2-sulfinyl)-5-fluoro-2-methyl-indol-1-yl]-acetic acid
[5-Fluoro-2-methyl-3-(quinoline-2-sulfonyl)-indol-1-yl]-acetic acid
[5-Fluoro-2-methyl-3-(quinolin-8-ylsulfonyl)-indol-1-yl]-acetic acid
(5-Fluoro-2-methyl-3-phenylmethanesulfonyl-1H-indol-1-yl)-acetic acid
[3-(4-Chloro-phenylsulfamoyl)-5-fluoro-2-methyl-indol-1-yl]-acetic acid
[3-(3-Chloro-phenylsulfamoyl)-5-fluoro-2-methyl-indol-1-yl]-acetic acid
[3-(4-Fluoro-phenylsulfamoyl)-5-fluoro-2-methyl-indol-1-yl]-acetic acid
[3-(2-Chloro-phenylsulfamoyl)-5-fluoro-2-methyl-indol-1-yl]-acetic acid
(3-Benzylsulfamoyl-5-fluoro-2-methyl-indol-1-yl)-acetic acid
[5-Fluoro-3-(2-methoxy-phenylsulfamoyl)-2-methyl-indol-1-yl]-acetic acid
[5-Fluoro-3-(4-methoxy-phenylsulfamoyl)-2-methyl-indol-1-yl]-acetic acid
(5-Fluoro-2-methyl-3-phenylsulfamoyl-indol-1-yl)-acetic acid
[3-(3,4-Dichloro-benzylsulfamoyl)-5-fluoro-2-methyl-indol-1-yl]-aceticacid
[5-Fluoro-3-(3-methoxy-phenylsulfamoyl)-2-methyl-indol-1-yl]-acetic acid
(5-Fluoro-2-methyl-3-*m*-tolylsulfamoyl-indol-1-yl)-acetic acid
(5-Fluoro-2-methyl-3-p-tolylsulfamoyl-indol-1-yl)-acetic acid
[3-(4-Chloro-benzylsulfamoyl)-5-fluoro-2-methyl-indol-1-yl]-acetic acid
[3-(Benzyl-methyl-sulfamoyl)-5-fluoro-2-methyl-indol-1-yl]-acetic acid

[5-Fluoro-2-methyl-3-(pyridin-3-ylsulfamoyl)-indol-1-yl]-acetic acid;

or the C_1-C_6 alkyl, aryl, $(CH_2)_mOC(=O)C_1$-C_6alkyl, $(CH_2)_mN(R^{11})_2$, $CH((CH_2)_mO(C=O)R^{12})_2$ esters of any of the above; wherein

m is 1 or 2;

R^{11} is hydrogen or methyl;

R^{12} is C_1-C_{18} alkyl.

17. A process for the preparation of a compound of general formula (I) as claimed in any one of claims 1 to 13 or 16 wherein n is 1 or 2 and X is a bond, the process comprising treating a compound of general formula (Ia), which is a compound of general formula (I) wherein n is 0 and X is a bond, by oxidation with a suitable oxidising agent.

18. A process for the preparation of a compound of general formula (I) as claimed in any one of claims 1 to 16, the process comprising reacting a compound of general formula (II) as defined in claim 2 and wherein R^{10} is C_1-C_6 alkyl with a base.

19. A compound as claimed in any one of claims 1 to 16 for use in medicine.

20. A compound as claimed in any one of claims 1 to 16 for use in the treatment of allergic asthma, perennial allergic rhinitis, seasonal allergic rhinitis, atopic dermatitis, contact hypersensitivity (including contact dermatitis), conjunctivitis, especially allergic conjunctivitis, eosinophilic bronchitis, food allergies, eosinophilic gastroenteritis, inflammatory bowel disease, ulcerative colitis and Crohn's disease, mastocytosis, another PGD_2-mediated disease, for example autoimmune diseases such as hyper IgE syndrome and systemic lupus erythematus, psoriasis, acne, multiple sclerosis, allograft rejection, reperfusion injury and chronic obstructive pulmonary disease; or rheumatoid arthritis, psoriatic arthritis or osteoarthritis.

21. The use of a compound as claimed in any one of claims 1 to 16 in the preparation of an agent for the treatment or prevention allergic asthma, perennial

allergic rhinitis, seasonal allergic rhinitis, atopic dermatitis, contact hypersensitivity (including contact dermatitis), conjunctivitis, especially allergic conjunctivitis, eosinophilic bronchitis, food allergies, eosinophilic gastroenteritis, inflammatory bowel disease, ulcerative colitis and Crohn's disease, mastocytosis, another PGD_2-mediated disease, for example autoimmune diseases such as hyper IgE syndrome and systemic lupus erythematus, psoriasis, acne, multiple sclerosis, allograft rejection, reperfusion injury and chronic obstructive pulmonary disease; or rheumatoid arthritis, psoriatic arthritis or osteoarthritis.

22. A pharmaceutical composition comprising a compound as claimed in any one of claims 1 to 16 together with a pharmaceutical excipient or carrier.

23. A composition as claimed in claim 22 formulated oral, rectal, nasal, bronchial (inhaled), topical (including eye drops, buccal and sublingual), vaginal or parenteral (including subcutaneous, intramuscular, intravenous and intradermal) administration.

24. A composition as claimed in claim 23 formulated for oral, nasal, bronchial or topical administration.

25. A composition as claimed in any one of claims 22 to 24 containing one or more additional active agents useful in the treatment of diseases and conditions mediated by PGD_2 at the CRTH2 receptor.

26. A composition as claimed in claim 25, wherein the additional active agents are selected from:

β2 agonists such as salmeterol;

corticosteroids such as fluticasone;

antihistamines such as loratidine;

leukotriene antagonists such as montelukast;

anti-IgE antibody therapies such as omalizumab;

anti-infectives such as fusidic acid (particularly for the treatment of atopic

dermatitis);
anti-fungals such as clotrimazole (particularly for the treatment of atopic dermatitis);
immunosuppressants such as tacrolimus and particularly pimecrolimus in the case of inflammatory skin disease;
other antagonists of PGD_2 acting at other receptors such as DP antagonists;
inhibitors of phoshodiesterase type 4 such as cilonilast;
drugs that modulate cytokine production such as inhibitors of TNFα converting enzyme (TACE);
drugs that modulate the activity of Th2 cytokines IL-4 and IL-5 such as blocking monoclonal antibodies and soluble receptors;
PPAR-γ agonists such as rosiglitazone;
5-lipoxygenase inhibitors such as zileuton.

27. A process for the preparation of a pharmaceutical composition as claimed in any one of claims 22 to 26 comprising bringing a compound as claimed in any one of claims 1 to 16 in conjunction or association with a pharmaceutically or veterinarily acceptable carrier or vehicle.

28. A product comprising a compound as claimed in any one of claims 1 to 16 and one or more of the agents listed in claim 26 as a combined preparation for simultaneous, separate or sequential use in the treatment of a disease or condition mediated by the action of PGD_2 at the CRTH2 receptor.

29. The use as claimed in claim 21, wherein the agent also comprises an additional active agent useful for the treatment of diseases and conditions mediated by PGD_2 at the CRTH2 and/or DP receptor.

30. The use as claimed in claim 29, wherein the additional active agent is one of the agents listed in claim 26.